DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 10, 2011 has been entered. Claim(s) 1, 2, 4-9, and 11-18 are pending. Claims 1, 2, 4, 9, 11-15, and 18 are under examination.

Claim Objections – New Grounds

Claims 1, 2, 4, 9, 11-15, and 18 are objected to because of the following informalities:

The term "Multiplex" should not be capitalized.

Appropriate correction is required.

Claim Rejections - 35 USC § 103 - Maintained

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1. Claim(s) 1, 2, 9, 11, 12, and 18 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Hsih et al. (J Food Prot. 2001 Nov;64(11):1744-50) in view of Kearney et al. (U.S. 5,589,335), and in further view of Brasher et al. (Curr Microbiol. 1998 Aug;37(2):101-7).

At the outset, it is noted that Applicant's amendments have been fully considered but do not overcome the instant rejection.

The examiner agrees that the claimed method *consists of* only a step for extracting DNA and a step for multiplex PCR.

However, as read by the examiner, the "extracting" step is recited in open language and such step is not defined by the specification to expressly exclude a separation step such as immunomagnetic separation. For example, the step requires

treating by "at least" the recited components which implies further components may be present or used. The specification does not recite that microbeads are excluded from those components.

Furthermore, as read by the examiner, Hish teaches immunomagnetic separation *outside* of a series of lysis and PCR steps. For example, Hsih teaches immunomagnetic separation, *followed by* cellular lysis (DNA extraction) and PCR (see pg. 1745, col. 2, teaches IMS *followed by* multiplex PCR, for example). Thus, Hish teaches a series of steps *consisting of* only a lysis step for extracting DNA and a step for multiplex PCR.

Hsih teaches methods of detecting *Salmonella typhimurium* and *Listeria monocytogenes* comprising: (a) extracting DNA; and (b) performing multiplex PCR (pg. 1745, col. 2, teaches creating a cell lysate and performing multiplex PCR, for example). The reference expressly teaches that UP broth was used such that both bacteria could grow simultaneously (pg. 1745, col. 1, culture conditions). The UP broth appears analogous to the medium No. 17 used by Applicant on pg. 23 of specification (0.5 g glucose).

Hsih does not expressly detail the methods used to create a cell lysate.

Thus, Hish does not expressly teach treating bacterial samples with a lytic enzyme, a surfactant, and a protein denaturant.

Kearney provides a supportive disclosure that teaches lysing a bacterial sample comprising *E. coli* and *L. monocytogenes* with lysozyme, bacteriocin, and proteinase K (col. 17, lines 50-65, for example).

None of the above references expressly teach the use of a surfactant during cellular lysis.

Brasher provides a supportive disclosure that teaches lysing a bacterial sample comprising *E. coli* and *S. typhimurium* with SDS and proteinase K followed by centrifugation and DNA precipitation with alcohol (pg. 102, col. 1, genomic DNA extraction, for example).

Thus, in summary, it is submitted that it would have been *prima facie* obvious to a person of ordinary skill in the art at the time of invention to utilize a combination of a lysozyme, bacteriocin, surfactant, and protein denaturant to lyse the bacterial samples of Hsih since the prior art exemplifies each reagent as useful for lysing the different types of bacteria in Hsih.

Applicant is reminded that the "teaching, suggestion, or motivation" (TSM) test should not be applied as a rigid formula for determination of obviousness. In a recent case before the Supreme Court, *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007), the court addressed the TSM test, reciting the following,

> "The obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion, and motivation, or by overemphasis on the importance of published articles and the explicit content of issued patents. The diversity of inventive pursuits and of modern technology counsels against limiting the analysis in this way. In many fields it may be that there is little discussion of obvious techniques or combinations, and it often may be the case that market demand, rather than scientific literature, will drive design trends. Granting patent protection to advances that would occur in the ordinary course without real innovation retards progress and may, in the case of patents combining previously known elements, deprive prior inventions of their value or utility."

Furthermore, in *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 80 USPQ2d 1641 (Fed. Cir. 2006), the court found that,

"Our suggestion test is in actuality quite flexible and not only permits, but requires, consideration of common knowledge and common sense,...,Indeed, we have repeatedly held that an implicit motivation to combine exists not only when a suggestion may be gleaned from the prior art as a whole, but when the "improvement" is technology-independent and the combination of references results in a product or process that is more desirable, for example because it is stronger, cheaper, cleaner, faster, lighter, smaller, more durable, or more efficient. Because the desire to enhance commercial opportunities by improving a product or process is universal—and even common-sensical—we have held that there exists in these situations a motivation to combine prior art references even absent any hint of suggestion in the references themselves. In such situations, the proper question is whether the ordinary artisan possesses knowledge and skills rendering him capable of combining the prior art references,...,Persons of varying degrees of skill not only possess varying bases of knowledge, they also possess varying levels of imagination and ingenuity in the relevant field, particularly with respect to problem-solving abilities."

Thus, the courts have concluded that any reasoned argument grounded in the analysis set forth in *Graham et al. v. John Deere Company of Kansas City et al.*, 148 USPQ 459 (U.S. 1966), may form the basis for a *prima facie* case of obviousness.

In the instant case, a person of ordinary skill in the art would have possessed the knowledge necessary to create the claimed lysis combination to lyse the different bacteria of Hsih in a reasonably predictable manner.

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive.

Applicant argues, "...the Patent Office failed to provide any rational underpinning to support its contention that a skilled artisan would use the lytic enzyme, a nonionic surfactant and a protein denaturant in a method of Hsih." The examiner respectfully disagrees.

Kearney clearly teaches that a reagent of lysozyme, bacteriocin, and proteinase K was acceptable for lysing a bacterial sample of *E. coli* and *L. monocytogenes.* Brasher clearly teaches that a reagent including SDS is acceptable for lysing a bacterial sample including *E. coli* and *S. typhimurium.* Hsih teaches a method that requires lysis of a bacterial sample including *S. typhimurium* and *L. monocytogenes.* Thus, by simple deductive reasoning a skilled artisan would have been able to surmise that SDS would have made an acceptable addition to the reagent of Kearny to provide for appropriate lysis of a bacterial sample comprising both *S. typhimurium* and *L. monocytogenes,* i.e. the bacterial sample within Hish. As noted previously, the courts have found that,

> "'A person of ordinary skill in the art is also a person of ordinary creativity, not an automaton.' *KSR*, 550 U.S. 82 USPQ2d at 1397. "[I]n many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle."Id. Office personnel may also take into account 'the inferences and creative steps that a person of ordinary skill in the art would employ.'Id. 82 USPQ2d at 1396."

In the instant case, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time of invention to add known lysis agents for known bacteria to the methods of Hsih to provide for the increased likelihood of obtaining an appropriate amount of DNA for subsequent amplification.

Furthermore, MPEP 2142 exemplifies certain rationales for establishing obviousness such as: 1) use of known technique to improve similar devices (methods, or products) in the same way; 2) applying a known technique to a known device (method, or product) ready for improvement to yield predictable results. In the instant case, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time of invention to add known lysis agents for known bacteria to the methods of

Hsih to provide for the increased likelihood of obtaining an appropriate amount of DNA for subsequent amplification.

In response to Applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the Applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). As outlined above, a person of ordinary skill in the art would have possessed the knowledge necessary to create the claimed lysis combination to lyse the different bacteria of Hsih in a reasonably predictable manner.

Applicant further asserts, "...a method with superior accuracy compared to that of official methods was required for the detection. The present multiple detection method filled that void and can detect with superior accuracy plural bacteria contained in foods, for example, without even using IMS."

First, as outlined above, the claimed invention is read to still encompass IMS within the recited step of extraction.

Furthermore, a secondary consideration such as latent properties (e.g. unexpected superior results) must be supported by objective evidence of a probative value (see MPEP 716.01).

Thus, the rejection is maintained.

2. Claim(s) 4 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Hsih et al. (J Food Prot. 2001 Nov;64(11):1744-50) in view of Kearney et al. (U.S. 5,589,335), in view of Brasher et al. (Curr Microbiol. 1998 Aug;37(2):101-7) as applied to claim 1 above, and in further view of Rimick et al. (U.S. 6,468,743 B1) , in view of Buck et al ("Design Strategies and Performance of Custom DNA Sequencing Primers" Biotechniques. 1999. 27(3): pages 528-536), and in further view of Lowe et al. (Nucleic Acids Research, Vol. 18, No. 7, page 1757-1761, 1990).

The teachings of the previously applied reference(s) have been outlined in the above rejections. The previously applied reference(s) do not expressly teach the primer sequences recited in SEQ ID NOs: 5 and 6.

However, it is first noted that the *L. monocytogenes* target sequence for example, the sequence from which the claimed oligonucleotides were derived, is a sequence that was well known at the time of invention (see Rimick SEQ ID NO: 59). Thus, the binding site of SEQ ID NOs: 5 for example is suggested within the sequence disclosed by Rimick (see alignment of Rimick SEQ ID NO: 59 with SEQ ID NO: 5 for example below).

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RESULT 2
AR238655
LOCUS       AR238655                 40 bp    DNA     linear   PAT 20-DEC-2002
DEFINITION  Sequence 59 from patent US 6468743.
ACCESSION   AR238655
VERSION     AR238655.1  GI:27283725
KEYWORDS    .
SOURCE      Unknown.
  ORGANISM  Unknown.
            Unclassified.
REFERENCE   1  (bases 1 to 40)
  AUTHORS   Romick,T.L. and Fraser,M.S.
  TITLE     PCR techniques for detecting microbial contaminants in foodstuffs
  JOURNAL   Patent: US 6468743-A 59 22-OCT-2002;
            ConAgra Grocery Products Company; Fullerton, CA
FEATURES             Location/Qualifiers
     source          1. .40
                     /organism="unknown"
                     /mol_type="genomic DNA"
ORIGIN

  Query Match             100.0%;  Score 20;  DB 2;  Length 40;
  Best Local Similarity   100.0%;  Pred. No. 10;
  Matches   20;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 CGGAGGTTCCGCAAAAGATG 20
              ||||||||||||||||||||
Db          1 CGGAGGTTCCGCAAAAGATG 20
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Applicant is directed to *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed sequences simply represent structural homologs of those sequences disclosed in the prior art, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed

primers (SEQ ID NOs: 5 and 6) is *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck provides a supporting disclosure that expressly presents evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

In addition to teachings of Buck, Lowe provides a supportive disclosure that teaches a method for designing primers and evaluating their performance wherein a computer program is used for rapid selection of oligonucleotide primers for polymerase

chain reaction (see page 1757, col. 1, abstract). The reference teaches that all primers designed for over 10 gene products were experimentally tested and the results showed that all the amplification products specified by the primers are of the predicted size and also hybridize with the appropriate cDNA or internal oligonucleotide probe (see page 1760, col. 2, paragraph 1).

As explained above, the claimed sequences simply represent structural homologs of those sequences disclosed in the prior art, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers (SEQ ID NOs: 5 and 6) are *prima facie* obvious over the cited references in the absence of secondary considerations.

Furthermore, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention, to combine the known *L. monocytogenes* nucleic acid sequences as taught by the prior art with a step of generating and designing primers as taught by Hsih to detect the presence of *L. monocytogenes* because such genomic sequences were known (Rimick) at the time the invention was made, and it is obvious to generate primers from known sequences as taught by Lowe. The ordinary artisan would have had a reasonable expectation of success that such primers or primer pairs generated using known sequences as taught by Rimick in view of Lowe to amplify *L. monocytogenes* sequences for detection because the claimed primers are functional equivalents of the sequences taught by Hsih, Rimick, and Lowe explicitly taught that all primers designed for over 10 gene products were experimentally tested and the results showed that all the amplification products specified by the primers are of the predicted

size (see page 1760, col. 2, paragraph 1). The ordinary artisan would have been motivated to generate a number of said primers and primer pairs for detection of *L. monocytogenes* sequences to provide flexibility and optimize experimentation. Selection of specific oligonucleotides for specific T_m represents routine optimization with regard to sequence, length and composition of the oligonucleotide. Such optimization parameters are explicitly recognized in Lowe (This clearly shows that every primer would have a reasonable expectation of success). As noted in *In re Aller*, 105 USPQ 233 at 235, more particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. Routine optimization is not considered inventive and no evidence has been presented that the primer selection performed was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

It is noted that a sufficient showing of a secondary consideration (e.g. unexpected results) would obviate this and any further rejection of this type. Submission of a secondary consideration such as latent properties must be supported by objective evidence of a probative value (see MPEP 716.01).

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive.

Applicant argues, "Based on the reasoning of the Patent Office, if the whole sequence, for example, of *Listeria monocytogenes* organism is known, then a specific method using an unknown primer for *Listeria moncytogenes* is *primafacie* obvious. This reasoning is incorrect. Those skilled in the art would not and could not specifically select the primer sequences of SEQ ID Nos. 5 and 6 of the present invention for the high sensitivity multi-organism detection method without undue experimentation." The examiner respectfully disagrees. As outline above, such reasoning is legally sound in situations where the primer is nothing more than a homolog of a known sequence that would be expected to function as intended, i.e. act as a primer.

With regard to the assertion of a "high sensitivity" multi-organism detection method, it is not supported by any evidence. As noted above, a secondary consideration such as latent properties (e.g. unexpected superior results) must be supported by objective evidence of a probative value (see MPEP 716.01). The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465,43 USPQ2d 1362 (Fed. Cir. 1997). See also MPEP 2145.

Thus, absent a secondary consideration, the rejection is maintained.

3. Claim(s) 14 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Hsih et al. (J Food Prot. 2001 Nov;64(11):1744-50) in view of Kearney et al. (U.S. 5,589,335), in view of Brasher et al. (Curr Microbiol. 1998

Aug;37(2):101-7) as applied to claim 1 above, and in further view of Bussey et al. (U.S. 6,011,148).

The teachings of the previously applied reference(s) have been outlined in the above rejections. The previously applied reference(s) do not expressly teach the use of Tween 20.

Bussey provides a supportive disclosure that teaches,

"...plasmid DNA may be isolated from bacterial sources using conventional procedures including lysis with alkali and/or detergents, e.g. SDS, NP40, Tween 20 and the like, mechanical methods, or boiling, followed by precipitation of proteins, chromosomal DNA and cell debris. (see Sambrook, et al., 1989; Carlson et al., 1995, Biotech. Bioeng. 48: 303-315; Hirt, 1967, J. Mol. Biol. 26: 365-369)." (col. 5)

Thus, in summary, it is submitted that it would have been *prima facie* obvious to a person of ordinary skill in the art at the time of invention to utilize Tween 20 in the lysis mixture of Hsih since the prior art highlights Tween 20 as a functional equivalent of SDS.

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive.

Applicant argues, "...to use Tween 20 in Bussey would rather teach away the use of Tween 20 in the present invention in which the amplification target is chromosomal DNA." The examiner respectfully disagrees. Furthermore, "the prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or

otherwise discourage the solution claimed...." *In re Fulton*, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004). Also see MPEP 2145. The prior art recognizes both SDS and Tween 20 as appropriate lysis reagents.

In fact, such disclosure further supports the rejection of claim 1. Bussey demonstrated that it was known that bacterial lysis reagents could be made up of different combinations of reagents such as alkalai *and/or* detergents. A person of ordinary skill in the art at the time of invention would have possessed the knowledge to provide for the appropriate combination of lysis reagents.

Thus, the rejection is maintained.

4. Claim(s) 15 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Hsih et al. (J Food Prot. 2001 Nov;64(11):1744-50) in view of Kearney et al. (U.S. 5,589,335), in view of Brasher et al. (Curr Microbiol. 1998 Aug;37(2):101-7) as applied to claim 1 above, and in further view of Anzar et al. (Syst Appl Microbiol. 2002 Apr;25(1):109-19).

The teachings of the previously applied reference(s) have been outlined in the above rejections. The previously applied reference(s) do not expressly teach the use of guanidium isothiocyanate.

Anzar provides a supportive disclosure that teaches lysing a bacterial sample comprising *L. monocytogenes* with guanidium isothiocyanate (pg. 110, col. 2, DNA isolation, for example).

Thus, in summary, it is submitted that it would have been *prima facie* obvious to a person of ordinary skill in the art at the time of invention to utilize guanidium isothiocyanate in the lysis mixture of Hsih since the prior art highlights guanidium isothiocyanate as a functional equivalent of proteinase K.

Response to Arguments

Applicant's arguments have been addressed in the response(s) set forth above.

5. Claim(s) 13 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Hsih et al. (J Food Prot. 2001 Nov;64(11):1744-50) in view of Kearney et al. (U.S. 5,589,335), in view of Brasher et al. (Curr Microbiol. 1998 Aug;37(2):101-7) as applied to claim 1 above, and in further view of Nilsen et al. (Appl Environ Microbiol. 2003 May;69(5):2975-84).

The teachings of the previously applied reference(s) have been outlined in the above rejections. The previously applied reference(s) do not expressly teach the use of enterolysin.

Nilsen provides a supportive disclosure that teaches Enterolysin A as a cell wall-degrading bateriocin (abstract, for example).

Thus, in summary, it is submitted that it would have been *prima facie* obvious to a person of ordinary skill in the art at the time of invention to utilize Enterolysin A in the lysis mixture of Hsih since the prior art highlights such protein as lysis agent.

Response to Arguments

Applicant did not address this rejection.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher M. Babic whose telephone number is 814-880-9945. The examiner can normally be reached on Monday-Friday 10:00AM to 6:00PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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